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(54) Title: UNSATURATED OXYALKYLENE ESTERS AND USES THEREOF			
(57) Abstract			
<p>This invention relates to compositions for and methods of treating, preventing or ameliorating cancer and other proliferative diseases as well as methods of inducing wound healing, treating cutaneous ulcers, treating gastrointestinal disorders, treating blood disorders such as anemias, immunomodulation, enhancing recombinant gene expression, treating insulin-dependent patients, treating cystic fibrosis patients, inhibiting telomerase activity, treating virus-associated tumors, especially EBV-associated tumors, modulating gene expression and particularly augmenting expression of a tumor suppressor gene and inducing tolerance to an antigen. The methods of the invention use unsaturated oxyalkylene esters.</p>			

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UNSATURATED OXYALKYLENE ESTERS AND USES THEREOF

FIELD OF THE INVENTION

5 This invention relates to compositions for and methods of treating, preventing or ameliorating cancer and other proliferative diseases as well as methods of inducing wound healing, treating cutaneous ulcers, treating gastrointestinal disorders, treating blood
10 disorders such as anemias, immunomodulation, enhancing recombinant gene expression, treating insulin-dependent patients, treating cystic fibrosis patients, inhibiting telomerase activity, treating virus-associated tumors, especially EBV-associated tumors, modulating gene
15 expression and particularly augmenting expression of tumor suppressor genes, inducing tolerance to antigens, treating, preventing or ameliorating protozoan infection or inhibiting histone deacetylase in cells. The compositions of the invention are to and the methods of
20 the invention use unsaturated oxyalkylene esters.

BACKGROUND OF THE INVENTION

Butyric acid (BA) is a natural product. It is supplied to mammals from two main sources: 1) the diet,
25 mainly from dairy fat, and 2) from the bacterial fermentation of unabsorbed carbohydrates in the colon, where it reaches mM concentrations (Cummings, Gut 22:763-779, 1982; Leder et al., Cell 5:319-322, 1975).

BA has been known for nearly the last three decades
30 to be a potent differentiating and antiproliferative agent in a wide spectra of neoplastic cells *in vitro* (Prasad, Life Sci. 27:1351-1358, 1980). In cancer cells, BA has been reported to induce cellular and biochemical changes, e.g., in cell morphology, enzyme activity,
35 receptor expression and cell-surface antigens (Nordenberg et al., Exp. Cell Res. 162:77-85, 1986; Nordenberg et al., Br. J. Cancer 56:493-497, 1987; and Fishman et al., J. Biol. Chem. 254:4342-4344, 1979).

Although BA or its sodium salt (sodium butyrate, SB) has been the subject of numerous studies, its mode of action is unclear. The most specific effect of butyric acid is inhibition of nuclear deacetylase(s), resulting in hyperacetylation of histones H3 and H4 (Riggs, et al., Nature 263:462-464, 1977). Increased histone acetylation, following treatment with BA has been correlated with changes in transcriptional activity and the differentiated state of cells (Thorne et al., Eur. J. Biochem. 193:701-713, 1990). BA also exerts other nuclear actions, including modifications in the extent of phosphorylation (Boffa et al., J. Biol. Chem. 256:9612-9621, 1981) and methylation (Haan et al., Cancer Res. 46:713-716, 1986). Other cellular organelles, e.g., cytoskeleton and membrane composition and function, have been shown to be affected by BA (Bourgeade et al., J. Interferon Res. 1:323-332, 1981). Modulations in the expression of oncogenes and suppressor genes by BA were demonstrated in several cell types. Toscani et al., reported alterations in c-myc, p53 thymidine kinase, c-fos and AP2 in 3T3 fibroblasts (Oncogene Res. 3:223-238, 1988). A decrease in the expression of c-myc and H-ras oncogenes in B16 melanoma and in c-myc in HL-60 promyelocytic leukemia was also reported (Prasad et al., Biochem. Cell Biol. 68:1250-1255, 1992; and Rabizadeh et al., FEBS Lett. 328:225-229, 1993).

BA has been reported to induce apoptosis, i.e., programmed cell death. SB has been shown to produce apoptosis *in vitro* in human colon carcinoma, leukemia and retinoblastoma cell lines (Bhatia et al., Cell Growth Diff. 6:937-944, 1995; Conway et al., Oncol. Res. 7:289-297, 1993; Hague et al.; Int. J. Cancer 60:400-406, 1995). Apoptosis is the physiological mechanism for the elimination of cells in a controlled and timely manner. Organisms maintain a delicate balance between cell proliferation and cell death, which when disrupted can

tip the balance between cancer, in the case of over accumulation of cells, and degenerative diseases, in the case of premature cell losses. Hence, inhibition of apoptosis can contribute to tumor growth and promote progression of neoplastic conditions.

The promising *in vitro* antitumor effects of BA and BA salts led to the initiation of clinical trials for the treatment of cancer patients with observed minimal or transient efficacy [Novogrodsky et al., Cancer 51:9-14, 1983; Rephaeli et al., Intl. J. Oncol. 4:1387-1391, 1994; Miller et al., Eur. J. Cancer Clin. Oncol. 23:1283-1287, 1987].

Clinical trials have been conducted for the treatment of β -globin disorders (e.g., β -thalassemia and sickle-cell anemia) using BA salts. The BA salts elevated expression of fetal hemoglobin (HbF), normally repressed in adults, and favorably modified the disease symptoms in these patients (Stamatoyannopoulos et al., Ann. Rev. Med. 43:497-521, 1992). In this regard, arginine butyrate (AB) has been used in clinical trials with moderate efficacy (Perrine et al., N. Eng. J. Med. 328:81-86, 1993; Sher et al., N. Eng. J. Med. 332:1606-1610, 1995). The reported side effects of AB included hypokalemia, headache, nausea and vomiting in β -thalassemia and sickle-cell anemia patients.

Butyric acid derivatives with antitumor activity and immunomodulatory properties have been reported in U.S. Patent 5,200,553 and by Nudelman et al., 1992, J. Med. Chem. 35:687-694. The most active butyric acid prodrug reported in these references was pivaloyloxymethyl butyrate (AN-9). Similar compounds were reported for treating hemoglobinopathies (U.S. Patent No. 5,569,675).

BA and/or its analogues have also been reported to increase the expression of transfected DNA (Carstea et al., 1993, Biophys. Biochem. Res. Comm. 192:649; Cheng et al., 1995, Am. J. Physical 268:L615-L624) and to induce

tumor-restricted gene expression by adenovirus vectors (Tang et al., 1994, Cancer Gene Therapy 1:15-20). Tributyrin has been reported to enhance the expression of a reporter gene in primary and immortalized cell lines (Smith et al., 1995, Biotechniques 18:852-835).

However, BA and its salts are normally metabolized rapidly and have very short half-lives *in vivo*, thus the achievement and maintenance of effective plasma concentrations are problems associated with BA and BA salts, particularly for *in vivo* uses. BA and BA salts have required large doses to achieve even minimal therapeutic effects. Because of the high dosage, fluid overload and mild alkalosis may occur. Patients receiving BA emanate an unpleasant odor that is socially unacceptable.

While BA salts have been shown to increase HbF expression, and appear to hold therapeutic promise with low toxicity in cancer patients, they nevertheless have shown low potency in *in vitro* assays and clinical trials. There remains a need to identify compounds as effective or more effective than BA or BA salts as differentiating or anti-proliferating agents for the treatment of cancers. Such compounds need to have higher potency than BA without the problems associated with BA (such as bad odor). This need can be addressed by therapeutic compounds that either deliver BA to cells in a longer acting form or which have similar activity as BA but a longer duration of effectiveness *in vivo*.

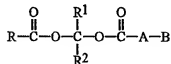
The compounds of this invention address these needs and are more potent than BA or BA salts for treating of cancers and other proliferative diseases, for treating gastrointestinal disorders, for wound healing, for treating blood disorders such as thalassemia, sickle cell anemia and other anemias, for modulating an immune response, for enhancing recombinant gene expression, for treating insulin-dependent patients, for treating cystic

fibrosis patients, for inhibiting telomerase activity, for treating virus-associated tumors, especially EBV-associated tumors, for modulating gene expression and particularly for augmenting expression of a tumor suppressor gene, for inducing tolerance to an antigen, for treating, preventing or ameliorating protozoan infection and for inhibiting histone deacetylase in cells.

Certain compounds used in the methods of this invention have been reported. For example, the use of substituted dicinnamic acid oxymethylene esters as sensitizers has been described in Japanese Patent No. 01128872 for use in thermal recording materials. The uses of substituted methoxy and hydroxy dicinnamic acid oxymethylene esters as anti-hepatotoxic agent have been described (Kiso et al, 1983, Planta Med. p. 185). Finally, German Patent No. 2,625,688 reports the use of butyl and cinnamic acid substituted oxymethylene esters as a anticholesteremic agent.

SUMMARY OF THE INVENTION

Accordingly, one embodiment of the present invention is directed to a method of treating preventing or ameliorating cancer and other proliferative disorders using compounds represented by Formula (I):



wherein

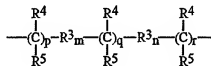
R is C₂-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, aryl or heteroaryl, any of which can be optionally substituted with halo, trifluoromethyl, hydroxy, alkoxy,

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cyano, nitro or carbonyl, wherein the heteroatom of said heteroaryl is oxygen or sulfur;

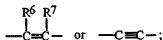
R^1 and R^2 are independently H, C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, or C_2 to C_{10} alkynyl, any of which can be optionally substituted with halo, alkoxy, amino, trifluoromethyl, aryl or heteroaryl;

A is



10

R^3 is independently



R^4 , R^5 , R^6 and R^7 are independently H, alkyl or alkenyl;

B is aryl or heteroaryl, wherein the heteroatom of said heteroaryl is oxygen or sulfur;

m and n are independently 0 to 5;

the sum of m and n is 1 to 5;

p, q and r are independently 0 to 2; or

a pharmaceutically-acceptable salt thereof;

with the proviso that when p, q and r are 0, each R^3 is $-CR^6=CR^7-$, R^6 is H or methyl and R^7 is H or methyl, then the sum of m and n can not be 4 or 5.

The above compounds can be used in all the methods of the invention. In a preferred embodiment, the compounds used in this and the other methods of the invention are those of Formula (I), wherein m is 1 to 5; n is 0 to 5; and p is 0. In another preferred embodiment, R^2 is H. Still more preferred are the compounds of Formula (I), wherein

R is n-propyl, benzyl, 3-(phenyl)propyl, 2-chloroethyl, 2-propenyl;

R¹ is H or alkyl;

5

R³ is



R⁶ and R⁷ are independently H or alkyl; and n, q and r are 0.

- 10 In a most preferred embodiment, the compounds are cinnamoyloxymethyl butyrate; cinnamoyloxymethyl phenylacetate; cinnamoyloxymethyl 4-phenylbutyrate; 1-(cinnamoyl)oxyethyl phenylacetate; 1-(cinnamoyl)oxyethyl 4-phenylbutyrate;
- 15 3,4-dimethoxycinnamoyloxymethyl butyrate; or 1-(3,4-dimethoxycinnamoyl)oxyethyl butyrate.

- The compounds of Formula (I) are particularly useful for methods of treating, preventing or ameliorating the effects of cancer and other proliferative disorders by acting as anti-proliferative or differentiating agents in subjects afflicted with such anomalies. Such disorders include, but are not limited, to leukemias, such as acute promyelocytic leukemia, acute myeloid leukemia, and acute myelomonocytic leukemia; other myelodysplastic syndromes,
- 25 multiple myeloma such as but not limited to breast carcinomas, cervical cancers, melanomas, colon cancers, nasopharyngeal carcinoma, non-Hodgkins lymphoma (NHL), Kaposi's sarcoma, ovarian cancers, pancreatic cancers, hepatocarcinomas, prostate cancers, squamous carcinomas,
- 30 other dermatologic malignancies, teratocarcinomas, T-cell lymphomas, lung tumors, gliomas, neuroblastomas, peripheral neuroectodermal tumors, rhabdomyosarcomas, and prostate tumors and other solid tumors. It is also possible that compounds of Formula (I) have anti-

proliferative effects on non-cancerous cells as well, and may be of use to treat benign tumors and other proliferative disorders such as psoriasis. Preferred is the method for treating or ameliorating leukemia, squamous cell carcinoma and neuroblastoma.

The invention is further directed to a method of treating blood disorders by administering a therapeutically-effective amount of a compound of Formula (I) to a patient.

The blood disorders treatable in accordance with the invention include, but are not limited to, thalassemias, sickle cell anemias, infectious anemias, aplastic anemias, hypoplastic and hypoproliferative anemias, sideroblastic anemias, myelophthisic anemias, antibody-mediated anemias, anemias due to chronic diseases and enzyme-deficiencies, and anemias due to blood loss, radiation therapy and chemotherapy. In this regard, these methods can include increasing hemoglobin content in blood by administering a therapeutically-effective amount of a compound of Formula (I) to a subject.

Another embodiment of the invention is directed to a method of modulating an immune response in a host by administering an amount of a compound of Formula I is effective to modulate said immune response.

Modulation of the immune response includes enhancing cytokine secretion, inhibiting or delaying apoptosis in polymorphonuclear cells, enhancing polymorphonuclear cell function by augmenting hematopoietic growth factor secretion, inducing expression of cell surface antigens in tumor cells, and enhancing progenitor cell recovery after bone marrow transplantation.

The pharmaceutical agents of the invention for the above method include, but are not limited to, cytokines, interleukins, anti-cancer agents, chemotherapeutic agents, antibodies, conjugated antibodies, immune stimulants, antibiotics, hormone

antagonists, and growth stimulants. The compounds of the invention can be administered prior to, after or concurrently with any of the agents.

Yet another embodiment of the invention is directed to a method of ameliorating the effects of a cytotoxic agent which comprises administering a therapeutically-effective amount of a cytotoxic agent with a compound of Formula (I) to a mammalian patient for a time and in an amount to induce growth arrest of rapidly-proliferating epithelial cells of the patient and thereby protect those cells from the cytotoxic effects of the agent. The cytotoxic agent can be a chemotherapeutic agent, an anticancer agent, or radiation therapy. Rapidly proliferating epithelial cells are found in hair follicles, the gastrointestinal tract and the bladder. Such cells include hair follicle cells, or intestinal crypt cells. Rapidly proliferating cells are also found in the bone marrow and include bone marrow stem cells. In accordance with the invention the cytotoxic agent and the compound of Formula (I) can be administered simultaneously, or the cytotoxic agent can be administered prior to or after the compound of the invention. Administration (simultaneously or separately) can be done systemically or topically as determined by the indication. In addition, when the cytotoxic agent is radiation therapy, the compounds of the invention can be administered to a cancer patient pre- or post-radiation therapy to treat or ameliorate the effects of cancer.

A still further embodiment of the invention is directed to a method of inducing wound healing, treating cutaneous ulcers or treating a gastrointestinal disorder by administering a therapeutically-effective amount of a compound of Formula (I) to a subject in need of such treatment. The cutaneous ulcers which can be treated in accordance with the methods of the invention include leg and decubitus ulcers, stasis ulcers, diabetic ulcers and

atherosclerotic ulcers. With respect to wound healing, the compounds are useful in treating abrasions, incisions, burns, and other wounds. Gastrointestinal disorders treatable by the methods of the invention
5 include colitis, inflammatory bowel disease, Crohn's disease and ulcerative colitis.

A further embodiment of the invention relates to a method of enhancing recombinant gene expression by treating a recombinant host cell containing an expression
10 system for a mammalian gene product of interest with an expression-enhancing amount of a compound of Formula (I), wherein said gene product is encoded by a butyric acid-responsive gene. The host cells can be mammalian cells, insect cells, yeast cells or bacterial cells and the
15 correspondingly known expression systems for each of these host cells. The gene product can be any protein or peptide of interest, expression of which can be regulated or altered by butyric acid or a butyric acid salt. A butyric acid-responsive gene is a gene that has a
20 promoter, enhancer element or other regulon that modulates expression of the gene under its control in response to butyric acid or a salt of butyric acid. For example, gene products contemplated for regulation in accordance with the invention include but are not limited
25 to tumor suppressor genes (such as p53) and the γ -globin chain of fetal hemoglobin.

Yet a further embodiment of the invention is directed to a method of treating, preventing or ameliorating symptoms in insulin-dependent patients by
30 administering an amount of a compound of Formula (I) effective to enhance insulin expression.

Yet another embodiment of the invention relates to a method of treating, preventing or ameliorating symptoms in cystic fibrosis patients by administering an amount of
35 a compound of Formula (I) effective to enhance chloride channel expression.

Still another method of the invention is directed to a method of inhibiting telomerase activity in cancer cells by administering a telomerase-inhibiting amount of a compound of Formula (I) to the cells, wherein the amount is effective to decrease the telomerase activity of the cells and thereby inhibit the malignant progression of the cells. This method can be applied to *in vivo* or *in vitro* cells.

Another embodiment of this invention is directed to a method of treating, preventing or ameliorating virus-associated tumors by pre-, post or co-administering a therapeutically-effective amount of a compound of Formula (I) with a therapeutically-effective amount of an antiviral agent. Antiviral agents contemplated for use in the invention include ganciclovir, acyclovir and fampiclovir, and preferably ganciclovir. The virus-associated tumors which can be treated, prevented or ameliorated in accordance with the invention include, but are not limited to, EBV-associated malignancy, Kaposi's sarcoma, AIDS-related lymphoma, hepatitis B-associated malignancy or hepatitis C associated malignancy. EBV-associated malignancies include nasopharyngeal carcinoma and non-Hodgkins' lymphoma and are preferred embodiments of the invention.

Further still, the invention provides a method of modulating gene expression by treating a host or host cells with an amount of a compound of Formula I effective to enhance, augment or repress the expression of a gene of interest, preferably a butyric acid responsive gene. When expression of the gene of interest is to be enhanced or augmented, the gene can encode a gene product which is or acts as a repressor of another gene, a tumor suppressor, an inducer of apoptosis or an inducer of differentiation. When expression of the gene of interest is to be repressed, the gene can encode a gene product which is or acts as an oncogene or an inhibitor of

apoptosis. For example, the bcl-2 gene encodes an inhibitor of apoptosis.

More particularly, the invention is directed to a method of augmenting gene expression, especially of a tumor suppressor gene, a butyric acid-responsive gene or a fetal hemoglobin gene, by treating a host or host cells with an expression-enhancing amount of a compound of Formula (I). Preferably the host is a cancer patient. This method of the invention thus includes augmenting tumor suppressor gene expression in conjunction with *ex vivo* or *in vivo* gene therapy, i.e., the compound of the invention can be co-administered to the host during administration of gene therapy vectors or administration of the *ex vivo* transfected cells. Similarly, the compounds of the invention can be used to treat cells during the transfection step of *ex vivo* gene therapy. The hosts of the method therefore include cancer patients or other patients under going gene therapy. The host cells of the invention include hematopoietic cells such as stem cells and progenitor cells, e.g., or any other cell type used in *ex vivo* gene therapy.

Yet another embodiment of the invention is directed to a method of inducing tolerance to an antigen which comprises administering a therapeutically-effective amount of compound of Formula (I). Preferably the antigen is a self-antigen. For example, the self-antigen can be associated with an autoimmune disease such as systemic lupus erythromatosus, rheumatoid arthritis, multiple schlerosis, myasthenia gravis or diabetes. Alternatively tolerance can be induced to one or more antigens present on transplanted a organ or cells.

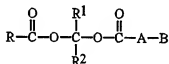
Yet further the invention is directed to a method for treating, preventing, or ameliorating protozoan infection in a subject which comprises administering to said subject an effective amount of a compound of Formula (I). The protozoan infections treatable in accordance

13

with the invention include, but are not limited to, malaria, cryptosporidiosis, toxoplasmosis, or coccidiosis.

Still further the invention is directed to a method of inhibiting histone deacetylase in cells which comprises administering an effective amount of a compound of Formula (I) to said cells.

The invention is also directed to compounds represented by the formula:

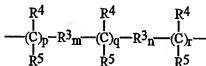


wherein

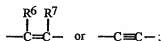
R is C₂ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₂ to C₁₀ alkynyl, aryl or heteroaryl, any of which can be optionally substituted with halo, trifluoromethyl, hydroxy, alkoxy, cyano, nitro or carbonyl, wherein the heteroatom of said heteroaryl is oxygen or sulfur;

R¹ and R² are independently H, C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, or C₂ to C₁₀ alkynyl, any of which can be optionally substituted with halo, alkoxy, amino, trifluoromethyl, aryl or heteroaryl;

A is



R³ is independently



R⁴, R⁵, R⁶ and R⁷ are independently H, alkyl or alkenyl;

14

B is aryl or heteroaryl, wherein the heteroatom of said heteroaryl is oxygen or sulfur;

m and n are independently 0 to 5;

the sum of m and n is 1 to 5;

5 p, q and r are independently 0 to 2; or
a pharmaceutically-acceptable salt thereof;

with the provisos that (1) when R is selected from the group of 2-phenylethenyl moieties consisting of 2-phenylethenyl, 2-(alkylphenyl)ethenyl, 2-(nitrophenyl)ethenyl or 2-(halophenyl)ethenyl, then A and B taken together cannot be any of said moieties; (2) that when R is p-hydroxyphenyl, then A and B taken together cannot be 2-(3-hydroxy-4-methoxyphenyl)ethenyl; and (3) that when p, q and r are 0, each R³ is -CR⁶=CR⁷-, R⁶ is H or methyl and R⁷ is H or methyl, then the sum of m and n cannot be 4 or 5.

In a preferred embodiment, the compounds of the invention are those of Formula (I), wherein m is 1 to 5; n is 0 to 5; and p is 0. In another preferred embodiment, R² is H. Still, more preferred are the compounds of Formula (I), wherein

R is n-propyl, benzyl, 3-(phenyl)propyl, 2-chloroethyl, 2-propenyl;

R¹ is H or alkyl;

25 R³ is



R⁶ and R⁷ are independently H or alkyl; and
n, q and r are 0.

In a most preferred embodiment, the compounds used in this invention are cinnamoyloxymethyl butyrate; cinnamoyloxymethyl phenylacetate; cinnamoyloxymethyl 4-phenylbutyrate; 1-(cinnamoyl)oxyethyl phenylacetate; 1-(cinnamoyl)oxyethyl 4-phenylbutyrate; 3,4-dimethoxycinnamoyloxymethyl butyrate; or

1-(3,4-dimethoxycinnamoyl)oxyethyl butyrate.

Another embodiment of the present invention is drawn to pharmaceutical compositions comprising a therapeutically effective amount of a compound of Formula (I) and a pharmaceutically effective carrier or diluent.

A further embodiment of the present invention is directed to pharmaceutical compositions comprising a therapeutically effective amount of a combination of compound of Formula (I) with other anti-cancer or anti-neoplastic agents together with a pharmaceutically effective carrier or diluent.

DETAILED DESCRIPTION OF THE INVENTION

The compounds herein described may contain asymmetric centers and geometric isomers. All chiral, diastereomeric, and racemic forms are included in the present invention. Many geometric isomers of olefins and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention.

By "stable compound" or "stable structure" is meant herein a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

As used herein, "alkyl" means both branched- and straight-chain, saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. As used herein "lower alkyl" means an alkyl group having 1 to 5 carbon atoms. As used herein, "alkenyl" means hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds, such as ethenyl, propenyl, and the like. "Lower alkenyl" is an alkenyl group having 2 to 6 carbon atoms. As used herein, "alkynyl" means hydrocarbon chains of either a straight or branched configuration and one or more

carbon-carbon triple bonds, such as ethynyl, propynyl and the like. "Lower alkynyl" is an alkynyl group having 2 to 6 carbon atoms. When the number of carbon atoms is not specified, then alkyl, alkenyl and alkynyl means lower alkyl, lower alkenyl and lower alkynyl, respectively.

As used herein, "aryl" includes "aryl" and "substituted aryl." Thus "aryl" of this invention means any stable 6- to 14-membered monocyclic, bicyclic or tricyclic ring, containing at least one aromatic carbon ring, for example, phenyl, naphthyl, indanyl, tetrahydronaphthyl (tetralinyl) and the like. The presence of substitution on the aryl group is optional, but when present, the substituents can be halo, alkyl, alkoxy, hydroxy, cyano, nitro or trifluoromethyl. When present on R in Formula (I), then the aryl substituents do not include amino, acylamino or carbamoyl.

As used herein, the term "heteroaryl" includes "heteroaryl" and "substituted heteroaryl." Thus "heteroaryl" of this invention means a stable 5- to 10-membered monocyclic or bicyclic heterocyclic ring which is aromatic, and which consists of carbon atoms and from 1 to 3 heteroatoms selected from the group consisting of N, O and S and wherein the nitrogen may optionally be quaternized, and including any bicyclic group in which any of the above-defined heteroaryl rings is fused to a benzene ring. The heteroaryl ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The presence of substitution on the heteroaryl group is optional and can be on a carbon atom, a nitrogen atom or other heteroatom if the resulting compound is stable and all the valencies of the atoms have been satisfied. When present, the substituents of the substituted heteroaryl groups are the same as for the substituted aryl groups and also include alkylammonium salts when the substituent is an alkyl group attached to the nitrogen atom of the heteroaryl

ring. These quarternized ammonium salts include halides, hydrohalides, sulfates, methosulfates, methanesulfates, toluenesulfates, nitrates, phosphates, maleates, acetates, lactates or any other pharmaceutically acceptable salt. Examples of heteroaryl groups include, but are not limited to furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, benzothienyl, indolyl, indolenyl, quinoliny, isoquinoliny and benzimidazolyl.

When a heteroaryl group is present on R or B in Formula I, then the heterotoms can not be nitrogen. Similarly, if this same heteroaryl group has any substituents, the substituents do not include amino, cyano, nitro, acylamino or carbamoyl, i.e., there can not be a nitrogen-containing substituent.

As used herein, "aralkyl" and "heteroaralkyl" refer to an aryl or heteroaryl group attached to an alkyl group. The aryl and heteroaryl groups of this moiety can optionally be substituted in accordance with the definitions herein.

The term "substituted", as used herein, means that one or more hydrogens on the designated atom are replaced with a selection from the indicated groups, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound.

The substituents of the invention include, as indicated, halo, hydroxy, alkyl, alkoxy, amino, cyano, nitro, trifluoromethyl, aryl, heteroaryl, trialkylammonium and salts thereof. These groups can be substituents for alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl and heteroaralkyl groups as indicated in accordance with the invention. A "halo" group is a halogen, and includes fluoro, chloro, bromo and iodo groups. The term "alkoxy" refers to an alkyl group having at least one oxygen substituent represented by R-O-.

As used herein, "therapeutically-effective amount" refers to that amount necessary to administer to a host to achieve an anti-tumor effect; to induce differentiation and/or inhibition of proliferation of malignant cancer cells, benign tumor cells or other proliferative cells; to aid in the chemoprevention of cancer; to promote wound healing; to treat a gastrointestinal disorder; to treat a blood disorder or increase the hemoglobin content of blood; to modulate an immune response; to enhance recombinant gene expression; to modulate gene expression; to augment expression of tumor suppressor genes; to enhance insulin expression; to enhance chloride channel expression; to induce tolerance to an antigen; to treat, prevent or ameliorate protozoan infection; or to inhibit histone deacetylase in cells. Methods of determining therapeutically-effective amounts are well known.

When the therapeutic or effective amount of the compound is for treating, preventing or ameliorating cancer or other proliferative disorder, then that amount can be an amount effective to inhibit histone deacetylase in the subject, patient or cancerous cells. Similarly, when the therapeutic or effective amount of the compound is for treating, preventing, or ameliorating protozoan infection then that amount can be an amount effective to inhibit protozoan histone deacetylase in the subject, patient or cancerous cells.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds that are modified by making acid or base salts. Examples include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids, and the like. Pharmaceutically acceptable salts include, but are not limited to, hydrohalides, sulfates, methosulfates,

methanesulfates, toluenesulfonates, nitrates, phosphates, maleates, acetates, lactates and the like.

Pharmaceutically-acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric or greater amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. The salts of the invention can also be prepared by ion exchange, for example. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference in its entirety.

The "pharmaceutical agents" for use in the methods of the invention related to the coadministration of compounds of Formula II and Formula III, include but are not limited to anticancer agents as well as differentiating agents. For example, the pharmaceutical agent can be a cytokine, an interleukin, an anti-cancer agent, a chemotherapeutic agent, an antibody, a conjugated antibody, an immune stimulant, an antibiotic, a hormone antagonist or a growth stimulant. The pharmaceutical agent can also be a cytotoxic agent. Cytotoxic agents include antiviral nucleoside antibiotics such as ganciclovir, acyclovir, and fampiclovir. Cytotoxic agents can also include radiation therapy.

As used herein, the "chemotherapeutic agents" include but are not limited to alkylating agents, purine and pyrimidine analogs, vinca and vinca-like alkaloids, etoposide and etoposide-like drugs, corticosteroids, nitrosoureas, antimetabolites, platinum-based cytotoxic drugs, hormonal antagonists, anti-androgens and antiestrogens.

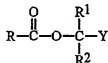
The "cytokines" for use herein include but are not limited to interferon, preferably α , β or γ interferon, as well as IL-2, IL-3, G-CSF, GM-CSF and EPO.

As used herein, an "immune stimulant" is a substance
 5 such as *C. parvum* or sarcolectin which stimulates a humoral or cellular component of the immune system.

The chemotherapeutic agents of the invention include but are not limited to tamoxifen, doxorubicin, L-asparaginase, dacarbazine, amascrine, procarbazine,
 10 hexamethylmelamine, mitoxantrone and gemcitabine.

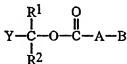
SYNTHETIC METHODS

The compounds of the present invention can generally be prepared by any method known in the art. For example,
 15 the compounds of the invention can be made by reacting the acid B-A-COOH with a reagent of the formula



or by reacting the acid RCOOH with the reagent of the
 formula

20



in the presence of a base, where Y is a leaving group such as halogen, methanesulfonate or *p*-toulenesulfonate and R, R¹, R², A and B are as defined herein. The above
 25 reagents are readily prepared according to literature procedures, see for example, Nudelman et al., J. Med. Chem. 35:687-694, 1992, and Japanese patent 07033709 (1995). The base can be a trialkylamine, pyridine, an alkali metal carbonate or other suitable base. The
 30 reaction can be carried out in the presence or absence of an inert solvent. Suitable solvents include, for

example, acetone, benzene, toluene, tetrahydrofuran, ethyl acetate, acetonitrile, dimethylformamide, dimethyl sulfoxide, chloroform, dioxan or 1,2-dichloroethane.

The procedures outlined above can be improved by one skilled in the art by, for instance, changing the temperature, duration, stoichiometry or other parameters of the reactions. Any such changes are intended to fall within the scope of this invention.

ACTIVITY

The activities of the compounds of the invention can be measured using generally-accepted techniques known to those skilled in the art consistent with the activity of interest. For example, the activity of compounds useful as differentiating agents can be measured using standard methodology of the nitro-blue tetrazolium reduction assay (e.g., Rabizadeh et al., FEBS Lett. 328:225-229, 1993; Chomienne et al., Leuk. Res. 10:631, 1986; and Breitman et al. in Methods for Serum-free Culture of Neuronal and Lymphoid Cells, Alan R. Liss, NY, p. 215-236, 1984 which are hereby incorporated by reference in their entirety) and as described below. This in vitro assay has been deemed to be predictive and in fact correlative with in vivo efficacy (Castaigne et al., Blood 76:1704-1709, 1990).

Another assay which is predictive of differentiating activity is the morphological examination for the presence of Auer rods and/or specific differentiation cell surface antigens in cells collected from treatment groups, as described in Chomienne et al., (Blood 76:1710-1717, 1990 which is hereby incorporated by reference in its entirety) and as described below.

The compounds of the present invention also have anti-proliferative and anti-tumor activity. The anti-proliferation activity of compounds of the present invention can be determined by methods generally known to

those skilled in the art. Generally-accepted assays for measuring viability and anti-proliferative activity are the trypan blue exclusion test and incorporation of tritiated thymidine, also as described by Chomienne, et al., above, which is incorporated herein by reference. Other assays which predict and correlate antitumor activity and *in vivo* efficacy are the human tumor colony forming assay described in Shoemaker et al., Can. Res. 45:2145-2153, 1985, and inhibition of telomerase activity as described by Hiyayama et al., J. Natl. Cancer Inst. 87:895-908, 1995, which are both incorporated herein by reference in their entirety. These assays are described in further detail below.

Cell Cultures

Human promyelocytic leukemia cells (HL-60), human pancreatic carcinoma cells (PaCa-2) and human breast adenocarcinoma cells, pleural effusion cells (MCF-7) can be cultured as follows. Cells are grown in RPMI media with 10% FCS, supplemented with 2 mM glutamine and incubated at 37°C in a humidified 5% CO₂ incubator. Alternatively, cells can be grown in any other appropriate growth medium and conditions which supports the growth of the cell line under investigation. Viability can be determined by trypan blue exclusion. Cells are exposed to a test compound, cultures are harvested at various time points following treatment and stained with trypan blue.

Cellular Staining to Detect Differentiation

Lipid staining and/or immunochemical staining of casein can be used as a marker for cellular differentiation of breast cancer cells (Bacus et al., Md. Carcin. 3:350-362, 1990). Casein detection can be done by histochemical staining of breast cancer cells using a human antibody to human casein as described by Cheung et

al., J. Clin. Invest. 75:1722-1728, which is incorporated by reference in its entirety.

Nitro-Blue Tetrazolium (NBT) Assay:

5 Cell differentiation of myeloid leukemia cells can be evaluated, for example, by NBT reduction activity as follows. Cell cultures are grown in the presence of a test compound for the desired time period. The culture medium is then brought to 0.1% NBT and the cells are
10 stimulated with 400 mM of 12-O-tetradecanoyl-phorbol-13-acetate (TPA). After incubation for 30 min at 37°C, the cells are examined microscopically by scoring at least 200 cells. The capacity for cells to reduce NBT is assessed as the percentage of cells containing
15 intracellular reduced black formazan deposits and corrected for viability.

Cell Surface Antigen Immunophenotyping

Cell surface antigen immunotyping can be conducted using dual-color fluorescence of cells gated according to size. The expression of a panel of antigens from early myeloid (CD33) to late myeloid can be determined as described in Warrell, Jr. et al., New Engl. J. Med. 324:1385-1392, 1992, which is incorporated by reference
25 herein in its entirety.

Apoptosis Evaluation

Apoptosis can be evaluated by DNA fragmentation, visible changes in nuclear structure or
30 immunocytochemical analysis of Bcl-2 expression.

DNA fragmentation can be monitored by the appearance of a DNA ladder on an agarose gel. For example, cellular DNA is isolated and analyzed by the method of Martin et al., J. Immunol., 145:1859-1867, 1990 which is
35 incorporated by reference herein in its entirety.

Changes in nuclear structure can be assessed, for example, by acridine orange staining method of Hare et al., J. Hist. Cyt., 34:215-220, 1986 which is incorporated by reference herein in its entirety.

5 Immunological detection of Bcl-2 can be performed on untreated cells and cells treated with the test compound. HL-60 cells are preferred but other cell lines capable of expressing Bcl-2 can be used. Cytospins are prepared and the cells are fixed with ethanol. Fixed cells are
10 reacted overnight at 4°C with the primary monoclonal antibody, anti-Bcl-2 at a dilution of 1:50. Staining is completed to visualize antibody binding, for example, using Strep A-B Universal Kit (Sigma) in accordance with the manufacturer's instructions. Identically-treated
15 cells which received no primary antibody can serve as a non-specific binding control. Commercial kits are also available and can be used for detecting apoptosis, for example, Oncor's Apop Tag®.

20 Modulation of Gene Expression

The levels of expression from oncogene and tumor suppressor genes can be evaluated by routine methods known in the art such as Northern blotting of RNA, immunoblotting of protein and PCR amplification.

25 Mouse Cancer Model

Compounds can be examined for their ability to increase the life span of animals bearing B16 melanomas, Lewis lung carcinomas and myelomonocytic leukemias as described in Nudelman et al., J. Med. Chem. 35:687-694, 1992, or Rephaeli et al., Int. J. Cancer 49:66-72, 1991, which are incorporated by reference herein in their
entireties.

For example, the efficacy of compounds of the
35 present invention in a leukemia model can be tested as follows: Balb/c mice are injected with WEHI cells and a

test compound or control solution is administered the following day. The life span of the treated animals is compared to that of untreated animals.

5 The efficacy of compounds of the present invention on primary tumors can also be tested with subcutaneously implanted lung carcinoma or B16 melanoma by measuring the mass of the tumor at the site of implantation every two weeks in control and treated animals.

10 The efficacy of compounds in xenografts can be determined by implanting the human tumor cells subcutaneously into athymic mice. Human tumor cell lines which can be used include, but are not limited to, prostate carcinoma (human Pc-3 cells), pancreatic carcinoma (human Mia PaCa cells), colon adenocarcinoma
15 (human HCT-15 cells) and mammary adenocarcinoma (human MX-1 cells). Treatment with control solution or a test compound of the invention begins, for example, when tumors are approximately 100 mg. Anti-tumor activity is assessed by measuring the delay in tumor growth, and/or
20 tumor shrinking and/or increased survival of the treated animals relative to control animals.

Telomerase Activity

25 High levels of telomerase activity is associated with the high proliferation rate found in cancer cells. Compounds which inhibit telomerase activity results in inhibition of cancer cell growth and de-differentiation. Commercially available telomerase assays can thus be used to assess the anticancer activities of compounds on
30 cancer cell lines.

Chemoprevention

The chemoprevention activity of the compounds of the invention can be determined in the two-stage mouse
35 carcinogenesis model of Nishimo et al. (supra).

Assay of Compounds

Compounds of the invention, their salts or metabolites, can be measured in a biological sample by any method known to those skilled in the art of pharmacology, clinical chemistry or the like. Such methods for measuring these compounds are standard methods and include, but are not limited to high performance liquid chromatography (HPLC), gas chromatography (GC), gas chromatography mass spectroscopy (GC-MS), radioimmunoassay (RIA), and others.

Dosage and Formulation

The compounds of the present invention can be administered to a mammalian patient to treat cancer or in any other method of the invention which involves treating a patient by any means that produces contact of the active agent with the agent's site of action in the body of the subject. Mammalian patients include humans and domestic animals. The compounds of the invention can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. The compounds can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. The pharmaceutical compositions of the invention may be adapted for oral, parenteral, transdermal, transmucosal, rectal or intranasal administration, and may be in unit dosage form, as is well known to those skilled in the pharmaceutical art. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques.

The appropriate dosage administered in any given case will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the

particular agent and its mode and route of administration; the age, general health, metabolism, weight of the recipient and other factors which influence response to the compound; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and the effect desired. A daily dosage of active ingredient can be expected to be about 10 to 10,000 milligrams per meter² of body mass (mg/m²), with the preferred dose being 50-5,000 mg/m² body mass.

Dosage forms (compositions suitable for administration) contain from about 1 mg to about 1 g of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid or semi-solid dosage forms, such as for example hard or soft-gelatin capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, disperse powders or granules, emulsions, and aqueous or oily suspensions. It can also be administered parenterally, in sterile liquid dosage forms. Other dosage forms include transdermal administration via a patch mechanism or ointment.

Compositions intended for oral use may be prepared according to any methods known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents, and preserving agents in order to provide a pharmaceutically elegant and palatable preparation.

Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. Such excipients may include, for example, inert diluents, such as calcium phosphate, calcium carbonate, sodium

carbonate, sodium phosphate, or lactose; granulating disintegrating agents, for example, maize starch or alginic acid; binding agents, such as starch, gelatin, or acacia; and lubricating agents, for example, magnesium stearate, stearic acids or talc. Compressed tablets may be uncoated or may be sugar coated or film coated by known techniques to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration and adsorption in the gastrointestinal tract.

Hard gelatin capsules or liquid filled soft gelatin capsules contain the active ingredient and inert powdered or liquid carriers, such as, but not limited to calcium carbonate, calcium phosphate, kaolin, lactose, lecithin starch, cellulose derivatives, magnesium stearate, stearic acid, arachis oil, liquid paraffin, olive oil, pharmaceutically-accepted synthetic oils and other diluents suitable for the manufacture of capsules. Both tablets and capsules can be manufactured as sustained release-products to provide for continuous release of medication over a period of hours.

Aqueous suspensions contain the active compound in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, e.g., sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth, and gum acacia; dispersing or wetting agents, such as a naturally occurring phosphatide, e.g., lecithin, or condensation products of an alkylene oxide with fatty acids, for example of polyoxyethylene stearate, or a condensation products of ethylene oxide with long chain aliphatic alcohols, e.g., heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, e.g., polyoxyethylene sorbitol monooleate, or a condensation

product of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, e.g., polyoxyethylene sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives, for example ethyl or *n*-propyl *p*-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin, or sodium or calcium cyclamate.

Dispersable powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring, and coloring agents, can also be present.

Syrups and elixirs can be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions can be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), polysorbate and related sugar solutions, emulsions, such as Intralipid® (Cutter Laboratories, Inc., Berkley CA) and glycols such as propylene glycol or polyethylene glycols are suitable

carriers for parenteral solutions. Antioxidizing agents, such as but not limited to sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used can be citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as but not limited to benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

The pharmaceutical compositions of the present invention also include compositions for delivery across cutaneous or mucosal epithelia including transdermal, intranasal, sublingual, buccal, and rectal administration. Such compositions may be part of a transdermal device, patch, topical formulation, gel, etc., with appropriate excipients. Thus, the compounds of the present invention can be compounded with a penetration-enhancing agent such as 1-n-dodecylazacyclopentan-2-one or the other penetration-enhancing agents disclosed in U.S. Patent Nos. 3,991,203 and 4,122,170 which are hereby incorporated by reference in their entirety to describe penetration-enhancing agents which can be included in the transdermal or intranasal compositions of this invention.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field, which is incorporated herein by reference in its entirety.

Various modifications of the invention in addition to those shown and described herein will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

The foregoing disclosure includes all the information deemed essential to enable those skilled in the art to practice the claimed invention. Because the cited patents or publications may provide further useful

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information these cited materials are hereby incorporated
by reference in their entirety.

EXAMPLE 1

Synthesis of 3,4-Dimethoxycinnamoyloxymethyl Butyrate
(DiMeOCOMB)

5 To a stirred solution of 3,4-dimethoxycinnamic acid
(5 g, 24 mmol) and chloromethyl butyrate (3.3 g, 1 eq.)
in dry dimethylformamide (20 mL), under nitrogen was
dropwise added triethylamine (4 mL, 2.3 g, 1.2 eq). The
10 reaction mixture was heated to 70°C overnight; during that
time a large amount of precipitate formed and TLC (ethyl
acetate:hexane 1:2) showed that all the acid had reacted.
The precipitate was filtered and washed with ethyl
acetate. The filtrate was partitioned between water and
ethyl acetate. The aqueous phase was washed with a small
15 amount of ethyl acetate, and the combined organic phase
was washed with water (3x), 5% solution of NaHCO₃ (2x),
and brine (2x), dried with MgSO₄ and evaporated to give
crude product as a yellow heavy oil (5.7 g). The crude
product was chromatographed on silica gel (200 g, ethyl
20 acetate:hexane 1:3) to give the pure product (second
fraction) as a colorless oil (4.7 g, 64% yield).

EXAMPLE 2

Synthesis of Cinnamoyloxymethyl Butyrate (COMB)

5 To a stirred solution of cinnamic acid (10 g, 67 mmol) and chloromethyl butyrate (9.5 g, 1 eq) in dry dimethylformamide (25 mL) under nitrogen was dropwise added triethylamine (12 mL, 8.5 g, 1.2 eq). The reaction mixture was heated at 70°C for 3 h; during that time a large amount of precipitate formed and TLC (ethyl acetate:hexane 1:4) showed that all the acid has reacted. The precipitate was filtered and washed with ethyl acetate. The filtrate was partitioned between water and ethyl acetate. The aqueous phase was washed with a small amount of ethyl acetate, and the combined organic phase was washed with water (3x), 5% solution of NaHCO₃ (2x) and brine (2x) dried with MgSO₄ and evaporated to give the crude product as an orange oil (15 g), which was distilled at 150°C/0.1-0.2 mm Hg. The pure product was obtained as a colorless oil (12 g, 72% yield).

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EXAMPLE 3

Additional Compounds of the Invention

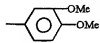
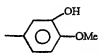

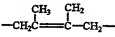

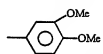
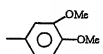
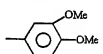
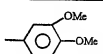
- 5 The compounds of Table 1 are those of Formula (I) having the specified groups and can be synthesized in a manner similar to that described above using the appropriate reagents.

10

TABLE 1

Additional Formula (I) Compounds of the Invention

R	R ¹	R ²	A	B
C ₆ H ₅ CH ₂ —	CH ₃	H		
ClCH ₂ CH ₂ CH ₂ —	CH ₃	C ₂ H ₅		
CH ₃ O—CH ₂ —C≡C—CH ₂ —	CCl ₃	H		
	C ₄ H ₉	H		
	CH ₃ CH=CH	H		
CF ₃ CH ₂ CH ₂ —	C ₆ H ₅	H		
C ₃ H ₇	CH ₃	H		

R	R ¹	R ²	A	B
C ₃ H ₇ —	GH ₇	H	—CH=CH—	
C ₃ H ₇ —	C ₃ H ₇	CH ₃	—C≡C—	
CH ₂ =CHCH ₂ —	C ₇ H ₁₉	H	—C≡C—CH=CH—	
C ₃ H ₇ —	C ₂ H ₅	H		
C ₆ H ₅ -CH ₂ -	H	H	-CH=CH-	
C ₆ H ₅ -CH ₂ -	CH ₃	H	-CH=CH-	
C ₆ H ₅ -CH ₂ CH ₂ CH ₂	H	H	-CH=CH-	
C ₆ H ₅ -CH ₂ CH ₂ CH ₂	CH ₃	H	-CH=CH-	
C ₆ H ₅ -CH ₂ -	H	H	-CH=CH-	C ₆ H ₅
C ₆ H ₅ -CH ₂ -	CH ₃	H	-CH=CH-	C ₆ H ₅
C ₆ H ₅ -CH ₂ CH ₂ CH ₂	H	H	-CH=CH-	C ₆ H ₅
C ₆ H ₅ -CH ₂ CH ₂ CH ₂	CH ₃	H	-CH=CH-	C ₆ H ₅

EXAMPLE 4

Inhibition of Cancer Cell Proliferation
Assessed by the SRB Assay

5 The inhibition of cell proliferation was measured in
the indicated cancer cell lines using the
sulforhodamine B (SRB) assay as described by Monks et
al., 1991, J. Natl. Can. Inst. 83:757-766. The SRB assay
is used to screen for anti-cancer drugs. The inhibitory
10 activities of COMB and DiMeOCOMB are compared to
 α -methylcinnamic acid (MeCA) and 2-methyl-3-
phenylpropionic acid (MePPA) in Table 2. The table
provides the dosage of each compound (in mM) which
inhibited fifty percent (IC_{50}) or ninety percent (IC_{90}) of
15 proliferation when calculated using the Chou Analysis'
Median Effective Dose equation.

37

TABLE 3
Inhibitory Activity of COMB and DiMeCOMB

5	Cell Line	MeCA		MePPA		COMB		DiMeOCOMB Butyrate	
		IC ₅₀	IC ₉₀	IC ₅₀	IC ₉₀	IC ₅₀	IC ₉₀	IC ₅₀	IC ₉₀
	CFPAC	1.938	>4.000	3.545	>4.0	0.150	0.237	0.308	3.570
	HL-60	2.602	>4.000	>4.000	>4.0	0.443	>4.000	0.203	0.248
	HT29	3.962	>4.000	>4.000	>4.0	0.349	0.492	0.406	0.798
10	LOX IMVI	3.356	>4.000	>4.000	>4.0	0.197	1.914	0.772	0.978
	MCF7	>4.000	>4.000	>4.000	>4.0	0.196	>4.000	0.301	0.466
	NCI-H23	3.271	>4.000	>4.000	>4.0	0.182	0.249	0.785	>4.000
	NCI-H522	1.979	3.818	>4.000	>4.0	0.189	0.249	0.752	1.366
	OVCAR-5	3.731	>4.000	>4.000	>4.0	0.367	0.500	1.464	1.892
15	PC-3	>4.000	>4.000	>4.000	>4.0	0.203	>4.000	1.441	1.874
	SF-295	>4.000	>4.000	>4.000	>4.0	0.197	>4.000	0.764	0.977

(a) All concentrations are in mM.

20

EXAMPLE 5
Inducing Differentiation

5 Cancer cell differentiation was evaluated in a human leukemia cell line by changes in expression of myelocytic maturation marker CD11b.

The level of CD11b was measured on HL-60 cells by flow cytometry using a monoclonal antibody (MAb) against CD11b in a standard indirect immunofluorescence assay. Cells
10 were cultured for 3 days with media or the indicated concentration of DiMeOCOMB. Cultured cells were collected by centrifugation, resuspended at 10^6 cells per 20μ RPMI+10% FCS and incubated with MAb for 30 min at 40°C . The cells were washed twice in cold PBS + 10% FCS and incubated with
15 a 1:20 dilution of FITC-conjugated F(ab')² fragment of rabbit anti-mouse IgG for 20-30 min at 40°C in the dark. After washing the cells twice in cold PBS + 10% FCS, the flow cytometry was performed. The results are shown in Table 3.

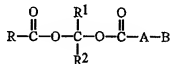
TABLE 3

Expression of CD11b

Concentration (μM)	% CD11b Cells
0	12.2
50	87.5
100	88.6
203	90.4

WE CLAIM:

1. A method of treating, preventing or ameliorating cancer or other proliferative disorder in a subject which comprises administering an amount of a compound effective to treat, prevent or ameliorate said cancer or said disorder, wherein said compound is represented by the formula:



10

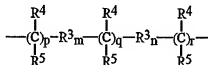
wherein

- R is C₂ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₂ to C₁₀ alkynyl, aryl or heteroaryl, any of which can be optionally substituted with halo, trifluoromethyl, hydroxy, alkoxy, cyano, nitro or carbonyl, wherein the heteroatom of said heteroaryl is oxygen or sulfur;

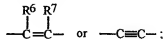
- R¹ and R² are independently H, C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, or C₂ to C₁₀ alkynyl, any of which can be optionally substituted with halo, alkoxy, amino, trifluoromethyl, aryl or heteroaryl;

20

A is

R³ is independently

25



R⁴, R⁵, R⁶ and R⁷ are independently H, alkyl or alkenyl;

- B is aryl or heteroaryl, wherein the heteroatom of said heteroaryl is oxygen or sulfur;

30

40

m and n are independently 0 to 5;
the sum of m and n is 1 to 5;
p, q and r are independently 0 to 2; or
a pharmaceutically-acceptable salt thereof;
5 with the proviso that when p, q and r are 0, each
 R^3 is $-CR^6=CR^7-$, R^6 is H or methyl and R^7 is H or methyl,
then the sum of m and n can not be 4 or 5.

10 2. The method of Claim 3, wherein
 R^2 is H.

3. The method of Claim 1, wherein
m is 1 to 5;
n is 0 to 5; and
15 p is 0.

4. The method of Claim 2, wherein
 R^2 is H.

20 5. The method of Claim 4, wherein in
R is n-propyl, benzyl, 3-(phenyl)propyl, 2-
chloroethyl, 2-propenyl;
 R^1 is H or alkyl;
 R^3 is



R^6 and R^7 are independently H or alkyl; and
n, q and r are 0.

6. The method of Claim 1, wherein said compound is
30 cinnamoyloxymethyl butyrate, cinnamoyloxymethyl
phenylacetate, cinnamoyloxymethyl 4-phenylbutyrate,
1-(cinnamoyl)oxyethyl phenylacetate,
1-(cinnamoyl)oxyethyl 4-phenylbutyrate,
3,4-dimethoxycinnamoyloxymethyl butyrate or

1-(3,4-dimethoxycinnamoyl)oxyethyl butyrate.

7. The method of anyone of Claims 1 to 6 wherein
5 said disorder is leukemia, squamous cell carcinoma,
prostate carcinoma, breast carcinoma, colon carcinoma,
pancreatic carcinoma, lung carcinoma, renal carcinoma,
neuroblastoma or melanoma.
- 10 8. The method of anyone of Claims 1 to 6 wherein said
compound is administered orally, parenterally,
transdermally, transmucosally, intranasally, rectally or
topically.
- 15 9. The method of any one of Claims 1 to 6, wherein
said effective amount is an amount effective to inhibit
histone deacetylase in said subject.
- 20 10. A method of differentiating or blocking
proliferation of cancerous or neoplastic cells comprising
administering to said cells an amount of a compound of any
one of Claims 1 to 6 effective to cause differentiation of
or to block proliferation of cancerous or neoplastic cells.
25
11. The method of Claim 10 wherein said cells are *in*
vivo.
- 30 12. The method of Claim 10 wherein said cells are *in*
vitro.
13. The method of Claim 10 wherein said compound is
administered orally, parenterally, transdermally,
35 transmucosally, intranasally, rectally or topically.

14. A method of increasing hemoglobin content in blood which comprises administering a therapeutically-effective amount of a compound of any one of Claims 1 to 6 to a subject.

5

15. The method of Claim 14 wherein said hemoglobin is fetal hemoglobin.

16. The method of Claim 14 wherein said composition is administered orally or parenterally.

17. A method of treating a blood disorder in a subject which comprises administering a therapeutically-effective amount of a compound of any one of Claims 1 to 6 to a subject.

15

18. The method of Claim 17, wherein treating said blood disorder comprises increasing the hemoglobin content in cells of said subject.

20

19. The method of Claim 17 wherein said disorder is selected from the group consisting of thalassemias, sickle cell anemias, infectious anemias, aplastic anemias, hypoplastic and hypoproliferative anemias, sideroblastic anemias, myelophthisic anemias, antibody-mediated anemias, anemias due to chronic diseases and enzyme-deficiencies, and anemias due to blood loss, radiation therapy and chemotherapy.

25

20. The method of Claim 17 wherein said composition is administered orally or parenterally.

30

21. A method of modulating an immune response in a host which comprises administering an amount of a compound of any one of Claims 1 to 6 effective to modulate said immune response.

35

22. The method of Claim 21 wherein modulating said immune response is enhancing cytokine secretion, inhibiting or delaying apoptosis in polymorphonuclear cells, enhancing polymorphonuclear cell function by augmenting hematopoietic growth factor secretion, inducing expression of cell surface antigens in tumor cells, enhancing progenitor cell recovery after bone marrow transplantation.

23. The method of Claim 21 wherein said compound is administered orally, parenterally, transdermally, transmucosally, intranasally, rectally or topically.

24. A method of treating, preventing or ameliorating cancer or other proliferative disorder in a subject in need of such treatment which comprises administering an amount of a compound of any one of Claims 1 to 6 effective to induce cellular apoptosis of the cancer cells or of the cells of the proliferative disorder.

25. The method of Claim 24 wherein said compound is administered orally, parenterally, transdermally, transmucosally, intranasally, rectally or topically.

26. A method for enhancing the actions of a pharmaceutical agent useful for the treatment of cancer and other proliferative disorders, comprising co-administering a therapeutically-effective amount of a compound of anyone of Claims 1 to 6 with a therapeutically-effective amount of said agent, wherein said agent is selected from the group consisting of a cytokine, an interleukin, an anti-cancer agent or an anti-neoplastic agent, a chemotherapeutic agent, an antibody, a conjugated antibody, an immune stimulant, an antibiotic, a hormone antagonist or a growth stimulant.

27. The method of Claim 26, wherein said antibiotic selected from the group consisting of ganciclovir, acyclovir, and famciclovir.

5 28. The method of Claim 26, wherein said chemotherapeutic agent is selected from the group consisting of an alkylating agent, a purine analog, a pyrimidine analog, a vinca alkaloid, a vinca-like alkaloid, etoposide, an etoposide-like drug, a corticosteroid, a
10 nitrosourea, an antimetabolite, a platinum-based cytotoxic drug, a hormonal antagonist, an anti-androgen and an anti-estrogen.

29. The method of Claim 26 wherein said cytokine is an
15 interferon.

30. The method of Claim 26 wherein said immune stimulant is *Corynebacterium parvum* or a sarcolectin.

20 31. The method of Claim 26 wherein the chemotherapeutic agent is selected from the group consisting of tamoxifen, doxorubicin, L-asparaginase, dacarbazine, amascrine, procarbazine, hexamethylmelamine, mitosantrone and gemcitabine.

25 32. The method of Claim 26 wherein said compound is administered orally, parenterally, transdermally, transmucosally, intranasally, rectally or topically.

30 33. A method of ameliorating the effects of a cytotoxic agent which comprises administering a therapeutically-effective amount of said cytotoxic agent with a compound of anyone of Claims 1 to 6 to a mammalian patient for a time and in an amount to induce growth arrest
35 of rapidly-proliferating epithelial cells or bone marrow

stem cells of said patient and thereby protecting said cells from cytotoxic effects of said agent.

34. The method of Claim 33, wherein said rapidly-
5 proliferating epithelial cells are in hair follicles, gastrointestinal tract or bladder.

35. The method of Claim 33, wherein said rapidly-
proliferating epithelial cells are hair follicle cells, or
10 intestinal crypt cells.

36. The method of Claim 33 wherein administering is simultaneous.

37. The method of Claim 33 wherein administering
15 comprises administering said agent before or after said compound.

38. The method of Claim 33 wherein said administration
20 is systemic or topical.

39. A method of treating gastrointestinal disorders
which comprises administering a therapeutically-effective
amount of a compound of anyone of Claims 1 to 6 to a
25 subject.

40. The method of Claim 39 wherein said compound is
administered orally, parenterally, transdermally,
transmucosally, intranasally, rectally or topically.
30

41. A method of treating cutaneous ulcers which
comprises administering a therapeutically-effective amount
of a compound of anyone of Claims 1 to 6 to a subject.

42. The method of Claim 41 wherein said compound is administered orally, parenterally, transdermally, transmucosally, intranasally, rectally or topically.

5 43. A method of inducing wound healing which comprises administering a therapeutically-effective amount of a compound of anyone of Claims 1 to 6 to a subject.

10 44. The method of Claim 43 wherein said compound is administered orally, parenterally, transdermally, transmucosally, intrasally, rectally or topically.

15 45. A method of enhancing recombinant gene expression which comprises treating a recombinant host cell containing an expression system for a gene product of interest with an expression-enhancing amount of a compound of anyone of Claims 1 to 6, wherein said gene product is encoded by a butyric acid-responsive gene.

20 46. The method of Claim 45, wherein said host cell is a mammalian cell, an insect cell, a yeast cell or a bacterial cell.

25 47. The method of Claim 45, wherein said gene product is a tumor suppressor gene or fetal hemoglobin.

30 48. A method of treating, preventing or ameliorating symptoms in insulin-dependent patients which comprises administering an amount of a compound of anyone of Claims 1 to 6 effective to enhance insulin expression.

35 49. The method of Claim 48 wherein said compound is administered orally, parenterally, transdermally, transmucosally, intranasally, rectally or topically.

50. A method of treating, preventing or ameliorating symptoms in cystic fibrosis patients which comprises administering an amount of a compound of anyone of Claims 1 to 6 effective to enhance chloride channel expression.

5

51. The method of Claim 50 wherein said compound is administered orally, parenterally, transdermally, transmucosally, intranasally, rectally or topically.

10

52. A method of inhibiting telomerase activity in cancer cells which comprises administering to said cells an amount of a compound of anyone of Claims 1 to 6 effective to decrease the basal level telomerase activity is said cells and thereby inhibit malignant progression of said cells.

15

53. The method of Claim 52 wherein said cells are *in vivo*.

20

54. The method of Claim 53 wherein said compound is administered orally, parenterally, transdermally, transmucosally, intranasally, rectally or topically.

25

55. The method of Claim 52 wherein said cells are *in vitro*.

30

56. A method of treating, preventing or ameliorating virus-associated tumors which comprises co-administering a therapeutically-effective amount of a compound of anyone of Claims 1 to 6 with a therapeutically-effective amount of an antiviral agent.

35

57. The method of Claim 56 wherein said antiviral agent is ganciclovir, acyclovir, or famciclovir.

58. The method of Claim 56 wherein said virus-associated tumor is an EBV-associated malignancy, Kaposi's sarcoma, an AIDS-related lymphoma, an hepatitis B-associated malignancy or an hepatitis C-associated malignancy.

59. The method of Claim 58 wherein said EBV-associated malignancy is nasopharyngeal carcinoma or non-Hodgkin's lymphoma.

60. The method of Claim 56 wherein said compound is administered orally, parenterally, transdermally, transmucosally, intranasally, rectally or topically.

61. A method of modulating gene expression which comprises treating a host or host cells with an amount of a compound of anyone of Claims 1 to 6 effective to enhance, augment or repress expression of a gene of interest.

62. The method of Claim 61 wherein expression of said gene is enhanced or augmented.

63. The method of Claim 62 wherein said gene encodes a gene product which is or acts as repressor, a tumor suppressor, an inducer of apoptosis or an inducer of differentiation.

64. The method of Claim 63 wherein said host is a cancer patient and said gene is a tumor suppressor gene.

65. The method of Claim 64 wherein said compound is administered orally, parenterally, transdermally, transmucosally, intranasally, rectally or topically.

66. The method of Claim 61 wherein expression of said gene is repressed.

67. The method of Claim 66 wherein said gene encodes a gene product which is or acts as an oncogene or an inhibitor of apoptosis.

5 68. The method of Claim 67 wherein said gene is bcl-2.

69. The method of Claim 61 wherein said host cells are undergoing ex vivo gene therapy.

10 70. The method of Claim 61 wherein said host is a patient receiving in vivo gene therapy.

71. The method of Claim 70 wherein said compound is administered orally, parenterally, transdermally, transmucosally, intranasally, rectally or topically.

72. A method of inducing tolerance to an antigen which comprises administering a therapeutically-effective amount of compound of anyone of Claims 1 to 6.

73. The method of Claim 72 wherein said antigen is a self-antigen.

25 74. The method of Claim 73 wherein said self-antigen is associated with an autoimmune disease.

75. The method of Claim 74 wherein said autoimmune disease is systemic lupus erythromatosus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis or diabetes.

76. The method of Claim 72 wherein said antigen is present on a transplanted organ or cells.

77. The method of Claim 72 wherein said compound is administered orally, parenterally, transdermally, transmucosally, intranasally, rectally or topically.

5 78. A method for treating, preventing, or ameliorating protozoan infection in a subject which comprises administering to said subject an effective amount of a compound of anyone of Claims 1 to 6.

10 79. The method of Claim 78, wherein said protozoan infection is malaria, cryptosporidiosis, toxoplasmosis, or coccidiosis.

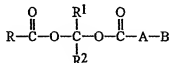
80. The method of Claim 78 wherein said compound is administered orally, parenterally, transmucosally, intranasally or rectally.

81. The method of Claim 78, wherein said effective amount is an amount of said compound effective to inhibit protozoan histone deacetylase in said subject.

82. A method of inhibiting histone deacetylase in cells which comprises administering an effective amount of a compound of anyone of Claims 1 to 6 to said cells.

25

83. A compound represented by the formula:



30 wherein

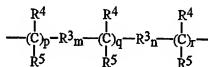
R is C₂ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₂ to C₁₀ alkynyl, aryl or heteroaryl, any of which can be optionally substituted with halo, trifluoromethyl, hydroxy, alkoxy,

51

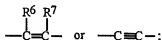
cyano, nitro or carbonyl, wherein the heteroatom of said heteroaryl is oxygen or sulfur;

- R^1 and R^2 are independently H, C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, or C_2 to C_{10} alkynyl, any of which can be optionally substituted with halo, alkoxy, amino, trifluoromethyl, aryl or heteroaryl;

A is



- 10 R^3 is independently



- 15 R^4 , R^5 , R^6 and R^7 are independently H, alkyl or alkenyl;

B is aryl or heteroaryl, wherein the heteroatom of said heteroaryl is oxygen or sulfur;

m and n are independently 0 to 5;

the sum of m and n is 1 to 5;

- 20 p, q and r are independently 0 to 2; or

a pharmaceutically-acceptable salt thereof;

with the provisos that (1) when R is selected

from the group of 2-phenylethenyl moieties consisting of 2-phenylethenyl, 2-(alkylphenyl)ethenyl, 2-

- 25 (nitrophenyl)ethenyl or 2-(halophenyl)ethenyl, then A and B taken together cannot be any of said moieties; (2) that when R is p-hydroxyphenyl, then A and B taken together cannot be 2-(3-hydroxy-4-methoxyphenyl)ethenyl; and (3) that when p, q and r are 0, each R^3 is $-CR^6=CR^7-$, R^6 is H or methyl and R^7 is H or methyl, then the sum of m and n can
30 not be 4 or 5.

84. The compound of Claim 83, wherein
R² is H.

5 85. The compound of Claim 83, wherein
 m is 1 to 5;
 n is 0 to 5; and
 p is 0.

10 86. The compound of Claim 85, wherein
 R² is H.

 87. The compound of Claim 86, wherein in
 R is n-propyl, benzyl, 3-(phenyl)propyl, 2-
15 chloroethyl, 2-propenyl;
 R¹ is H or alkyl;
 R³ is



 R⁶ and R⁷ are independently H or alkyl; and
20 n, q and r are 0.

 88. The compound of Claim 87, wherein said compound
is cinnamoyloxymethyl butyrate, cinnamoyloxymethyl
phenylacetate, cinnamoyloxymethyl 4-phenylbutyrate,
25 1-(cinnamoyl)oxyethyl phenylacetate,
1-(cinnamoyl)oxyethyl 4-phenylbutyrate,
3,4-dimethoxycinnamoyloxymethyl butyrate or
1-(3,4-dimethoxycinnamoyl)oxyethyl butyrate.

30 89. A pharmaceutical composition comprising a
therapeutically-effective amount of a compound of any one
of Claims 83 to 88 and a pharmaceutically-effective carrier
or diluent.

90. A pharmaceutical composition comprising a therapeutically-effective amount of a compound of any one of Claims 83 to 88 with a therapeutically-effective amount of a pharmaceutical agent, wherein said agent is selected from the group consisting of a cytokine, an interleukin, an anti-cancer agent or anti-neoplastic agent, a chemotherapeutic agent, an antibody, a conjugated antibody, an immune stimulant, an antibiotic, a hormone antagonist and a growth stimulant.
91. The composition of Claim 90 wherein said pharmaceutical agent comprises a cytotoxic agent.
92. The composition of Claim 90 wherein said antibiotic is an antiviral nucleoside antibiotic selected from the group consisting of ganciclovir, acyclovir, and famciclovir.
93. The composition of Claim 90 wherein said antibiotic is ganciclovir.
94. The composition of Claim 90 wherein said chemotherapeutic agent is selected from the group consisting of alkylating agents, purine and pyrimidine analogs, vinca and vinca-like alkaloids, etoposides and etoposide-like drugs, corticosteroids, nitrosoureas, antimetabolites, platinum based cytotoxic drugs, hormonal antagonists, anti-androgens and antiestrogens.
95. The composition of Claim 90, wherein said cytokine is an interferon.
96. The composition of Claim 90, wherein said immune stimulant is *Corynebacterium parvum* or a sarcolectin.

97. The composition of Claim 90, wherein the chemotherapeutic agent is selected from the group consisting of tamoxifen, doxorubicin, L-asparaginase, dacarbazine, amsacrine, procarbazine, hexamethylmelamine, mitoxantrone and gemcitabine.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/04756

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) : A01N 37/10; C07C 69/76 US CL : 514/533; 560/104 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/533; 560/104 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) STN CAS file Registry - STRUCTURE SEARCH		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DT 26 25 688 A1 (H. GRILL ET AL.) 22 December 1977, entire reference.	83-86, 89, 90
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:	*T*	Later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search	Date of mailing of the international search report	
08 JULY 1998	28 JUL 1998	
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